Amendments to the Specification:

Please replace the title of the application with the following:

NUCLEIC ACID MOLECULE ENCODING A CLASP-2 TRANSMEMBRANE PROTEIN

Please replace the paragraph beginning at pg. 2, line 29, with the following amended paragraph:

The ectodomain of the pre-formed synapse or "immune gateway" was recently discovered and is created in part by CLASP-1 (U.S.S.N. 09/411,328, filed October 1, 1999 (abandoned); ~~PCT/US99/22996~~WO00/20434). In addition to cadherin motifs, CLASP-1 also contains a CRK-SH3 binding domain, tyrosine phosphorylation sites, and coiled/coil domains suggesting direct interaction with cytoskeleton and regulation by adaptor molecules such as CRK. The *CLASP-1* transcript is present in lymphoid organs and neural tissue, and the protein is expressed by T and B lymphocytes and macrophages in the MOMA-1 subregion of the marginal zone of the spleen, an area known to be important in T: B cell interaction. CLASP-1 staining of individual T and B cells exhibits a preactivation structural polarity, being organized as a "ball" or "cap" structure in B cells, and forming a "ring", "ball" or "cap" structure in T cells. The placement of these structures is adjacent to the microtubule-organizing center ("MTOC"). CLASP-1 antibody staining indicates that CLASP-1 is at the interface of T-B cell conjugates that are fully committed to differentiation. Antibodies to the extracellular domain of CLASP-1 also block T-B cell conjugate formation and T cell activation.

Please replace the paragraph following section 5.2.3, beginning at page 37, line 21, with the following amended paragraph:

As is illustrated in FIG. 5, CLASP-2 is a member of a superfamily of immune-cell associated proteins with similar motifs. CLASP-1 was described in U.S.S.N. 09/411,328, filed October 1, 1999 (abandoned). CLASP-1 uniquely among the known CLASPs contains SH3 binding domain motifs. CLASP-2A, -B, -C, and -E polypeptides have no adaptor binding sites or SH3 binding domains found in CLASP-1. CLASP-3, CLASP-4, CLASP-5 and CLASP-7 are

described in ~~copending~~ U.S.S.N. 60/182,296, filed February 14, 2000 (expired), and which is incorporated by reference herein in its entirely for all purposes.

Please replace the paragraph beginning at page 126, lines 16-21, with the following amended paragraph:

All publications and patent documents cited above are hereby incorporated by reference in their entirety for all purposes to the same extent as if each were so individually denoted. Without wishing to exclude incorporating the remainder of the following patent applications, the following sections of the following patent applications are explicitly incorporated by reference herein: Figs 1-8, Table 2, the sequence listing and Examples 1-6 on pages 109-120 of USPN 09/737,246, filed December 13, 2000 (abandoned); Figs 1-8, Table 2, the sequence listing and Examples 1-6 on pages 108-119 of USPN 09/736,969, filed May 7, 2001 (abandoned); Figs. 1-8, Table 2, the sequence listing and Examples 1-4 on pages 106-111 of USPN 09/736,960 filed December 13, 2000 (abandoned); Figs. 1-7, Table 2, the sequence listing and Examples 1-4 on pages 106-111 of USPN 09/736,968, filed December 13, 2000 (abandoned); Figs. 1-9, Table 2, the sequence listing, and Examples 1-7 on pages 106-130 of USPN 09/978,244 filed October 15, 2001 (abandoned); and Figs 1-9, Table 2 and 3, the sequence listing and Examples 1-7 on pages –108-132 of PCT application serial no US02/24482 now published as WO03/025120.

Please replace the paragraph below Example 6B, beginning at page 119, line 5, with the following amended paragraph:

Similar methods have been used to construct fusions for expression of full length hCLASP-2 isoforms as well as truncated C-terminal forms in other cell lines such as Jurkat. Recombinant hCLASP-2 fragments were either isolated by digestion of cDNA clones or amplified by primers flanking specific regions ~~(Please provide some specific regions)~~. These can be cloned into expression vectors such as pBJ1-neo (Mark Davis, Stanford University), Peak12 (B. Seed, Harvard University), and pDsRed1-N1 (Clontech). pBJ1-neo and Peak12 allow untagged expression of recombinant proteins and pDsRed1-N1 will allow either untagged or a C-terminal Red fluorescent protein tag. These can be used to generate protein or for expression of various forms for functional analyses.

Please replace the paragraph beginning at page 120, line 7, with the following amended paragraph:

Media and solutions: RPMI 1640 medium, BioWhitaker; DMEM/M199 medium, BioWhitaker; EMEM, BioWhitaker; Fetal Bovine Serum, Summit (stored frozen at -20°C, stored thawed at 4°C); Trypsin-EDTA, GIBCO ~~(catalogue #25300-054)~~ (stored frozen at -20°C, stored thawed 4°C; Isoton II (stored at RT); DMSO (stored at RT); oligonucleotides (see Table 1 and FIG. 3, stored in solution at -20°C); PBS (Ca^{2+}/Mg^{2+} free); TE; 10 mM Tris-HCL, pH 8.0; 1 mM EDTA.

Please replace the paragraph beginning at page 16, line 19, with the following amended paragraph:

Another preferred example of algorithm that is suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.*, 1977, Nuc. Acids Res. 25: 3389-3402 and Altschul *et al.*, 1990, J. Mol. Biol. 215: 403-410, respectively. BLAST and BLAST 2.0 are used, with the parameters described herein, to determine percent sequence identity for the nucleic acids and proteins of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information ~~(http://www.ncbi.nlm.nih.gov/)~~. This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence.

Please replace the paragraph beginning on page 7, line 9, with the following amended paragraph:

FIG. 2[[.]]A. Schematic of CLASP-2 splice variants. Splice variants are compared to Human (h) CLASP-2A. Numbers above hCLASP-2A line diagram indicate where splice variations comprising deletions and insertions relative to hCLASP-2A are found. Abbreviations: "KIAA" KIAA1058 sequence (Genbank Accession No. AB028981). 2B. Nucleotide and predicted amino acid sequence of CLASP-2A cDNA. Notable protein motifs are

indicated above the nucleotide sequence in bold. Exact position of insertions and deletions are indicated above the CLASP-2A sequence with arrows and "x", respectively. The nucleotide sequence of insertions schematized in FIG. 2A are indicated above the arrow. The insertions and deletions are as follows (numeration refers to Human CLASP-2A nucleotide sequence): Nucleotides 1966-2034 are deleted in CLASP-2D. Nucleotides 2219-2224 are deleted in CLASP-2B. There is an insertion of 69 amino acids at nucleotide 2927 found in CLASP-2D. The nucleotide sequence for this insertion is:
AAGCAGTCCAGTGGGAGCCGCCCCTTCTCCCCCACAGCCATAGCGCCTGCCTGAG
GAGGAGCCGGGGAG (SEQ ID NO:11) and encodes amino acids
AVQWEPPLLPHSHSACLRRSRG (SEQ ID NO:12) (one letter amino acid abbreviation). This amino acid sequence encodes a putative SH3 binding domain. There is another deletion at between nucleotides 3011-3079 found in CLASP-2E. CLASPs 2B, 2C, 2D and 2E contain an insertion at nucleotide 3153 with the nucleotide sequence of:
TGAGAGGCTGGCCCATCTGTATGACACGCTGCACCGGGCCTACAGCAAAGTGAC
CGAGGTCATGCACTCGGGCCGCAGGCTTCTGGGGACCTACTTCCGGGTAGCCTTC
TTCGGGCAGGCAGCGCAATACCAGTTTACAGACAGTGAAACAGATGTGGAGGGA TT
(SEQ ID NO:13). The entire sequence is found in CLASP-2D and encodes amino acids
ERLAHLYDTLHRAYSKVTEVMHSGRRLLGTYFRVAFFGQAAQYQFTDSETDVEG (SEQ ID NO:14) while the underline sequence is found in CLASPs 2B, 2C, and 2E and encodes amino acids ERLAHLYDTLHRAYSKVTEVMHSGRRLLGTYFRVAFFGQG (SEQ ID NO:15). This amino acid sequence encodes a putative immunoreceptor tyrosine-based activation motif (ITAM). There is a two nucleotide deletion in Human CLASP-2C found at nucleotides 3586 and 3587. There is an insertion of 8 nucleotides found only in Human CLASP-2D with sequence: CTGGGATG at nucleotide 3937. This insertion puts a stop codon into the CLASP-2D nucleotide sequence.

Please replace the paragraph beginning on page 10, line 8, with the following amended paragraph:

FIG. 9[[.]]A. Binding of CLASP-2 C-terminal 20 amino acids to PDZ domains. 20 .mu.M biotinylated synthetic peptide corresponding to the C-terminal 20 amino acids of

CLASP-2 was reacted with the indicated plate bound GST fusion proteins (none=no GST fusion protein coated onto plate). Error bars indicate standard deviation of duplicate measurements. FIG. 9B. Affinity of CLASP 2-PDZ interactions. Varying concentrations of biotinylated CLASP-2 peptide were reacted with plate bound GST alone, GST-DLG1, GST-NeDLG, and GST-PSD95 fusion proteins. The binding to GST alone (<0.1 OD units) was subtracted from the binding to the fusion proteins and the remaining signal was divided by the signal observed upon addition of 30 μM CLASP-2 peptide to each PDZ domain-containing protein (0.4-1.0 OD units) and plotted. The plotted data was fit to a saturation binding curve, yielding an apparent affinity of 7.5 μM for NeDLG-CLASP-2 interaction, 21 μM for DLG1-CLASP-2 interaction, and 45 μM for PSD95-CLASP-2 interaction. Data are means of duplicate data points, with standard errors between duplicate data points <10%. FIG. 9C. Inhibition of CLASP-2-PDZ binding. 5 μM biotinylated synthetic peptide corresponding to the C-terminal 20 amino acids of CLASP-2 was reacted with the indicated, plate-bound PDZ domain-containing GST fusion proteins in the presence or absence of 100 μM competitor peptide. CLASP-2 Inhibitor refers to a synthetic peptide composed of the eight C-terminal amino acids of CLASP-2. KV1.3 Inhibitor refers to a synthetic peptide composed of the 19 C-terminal amino acids of KV1.3, a lymphocyte potassium channel. The amino acid sequence of the KV1.3 inhibitor is TTNNNPNSAVNIKKIFTDV (SEQ ID NO:86). FIG. 9D. Inhibition of KV1.3-PDZ binding. 5 μM biotinylated synthetic peptide corresponding to the C-terminal 19 amino acids of KV1.3 was reacted with the indicated, plate-bound PDZ-domain containing GST fusion proteins in the presence or absence of 100 μM CLASP-2 Inhibitor (see FIG. 9C legend).

Please replace the paragraph beginning on page 25, line 31, with the following amended paragraph:

If the predicted membrane spanning stretches do indeed function as transmembrane domains (see 5.2.1.3), then the putative CLASP extracellular domains are characterized by one cadherin EC-like motif (Pigott, R. and Power, C., 1993, The Adhesion Molecule Factbook. Academic Press, pg. 6; Jackson, R. M. and Russell, R. B., 2000, J. Mol. Biol. 296: 325-34). Several highly conserved cysteines are found in the extracellular domain, as

well as various glycosylation signals. Through its putative extracellular domains, CLASP proteins may interact with ligands in a homotypic and/or heterotypic manner to establish the immunological synapse in conjunction with molecules such as TCR, MHC class I, MHC class II, CD3 complex and accessory molecules such as CD4, CD3, ICAM-1, LFA-1, and others. Many cadherins contain a pro-domain of approximately 50 to 150 amino acids that is removed before localization to the plasma membrane. This cleavage is presumed to be carried out by Furin (Posthaus, H. et al., 1998, FEBS Let 438: 306-10) at a consensus sequence of RKQR (SEQ ID NO:89). Furin is a protease that is at least partially responsible for the maturation of certain cadherins. CLASP-2 has the sequence RNQR (SEQ ID NO:90) at nucleotides 854 through 865 (FIG. 1). By homology, this region is around 120 amino acids into the predicted protein start site for hCLASP-2A. This region may be a pro-domain and cleavage may be required for CLASP function, or aspects of CLASP function.

Please replace the paragraph beginning on page 29, line 4, with the following amended paragraph:

CLASP polypeptides contain a new "DOCK" motif, not previously described in the scientific literature. The CLASP DOCK motif includes a series of five tyrosines surrounded by conserved sequences in regions A, B, C, D, and G (see FIG. 5B). There are also two highly conserved non-tyrosine containing regions (E and G) separated by nine amino acids (P+EXAI+XM)(SEQ ID NO:91) and (LXMXL+GXVXXXVNXG)(SEQ ID NO:92) (where X is any amino acid).

Please replace the paragraph beginning on page 40, line 26, with the following amended paragraph:

For example, CLASP-2A and CLASP-2C are related to each other as apparent splice variants, with CLASP-2C containing an exon not found in CLASP-2A. The exon sequence is 5'-AGG GAT TTT GAG AGG CTG GCC CAT CTG TAT GAC ACG CTG CAC CGG GCC TAC AGC AAA GTG ACC GAG GTC ATG CAC TCG GGC CGC AGT TNC TGG GGA CCT ACT TCC GGG TAG CCT TCT TCG GGC AG-3' (SEQ ID NO:93) (encoding the peptide sequence: RDFERLAHLYDTLHRAYSKVTEVMHSGRRLLGTYFRVAFFGQGF) (SEQ ID NO:94). It will be apparent to one of skill that, by using polynucleotide probes or primers

corresponding to the nucleic acid sequence above, or by using antibodies that specifically recognize the peptide above, or those polynucleotide probes or primers shown in Table 3 below, it is possible to distinguish between different CLASP isoforms (e.g., to detect differential expression).

Please replace Table 3 beginning on page 41, line 3, with the following amended paragraph:

Table 3

	Found in/will detect	Exemplary Probe/Primer (5'-3')	Notes/Comments
1	full length hC2A	F1: CCCAGATTTTTATGATGAG (SEQ ID NO:95) R1: GATAATGACAAAGTTCTGAC (SEQ ID NO:96)	
2	full length hC2D	F2: CTGGAAATCTTGACAAAAATGC (SEQ ID NO:97) R2: GTCTTTTTAATACAGATGTGG (SEQ ID NO:98)	
3	hC2B, hC2C, hC2E	F3: GAGAGGCTGGCCCATCTGTATG (SEQ ID NO:99) R3: ATCTTCAAAGAATCCCTGCC (SEQ ID NO:100)	Distinction based upon product size differences following PCR
4	hC2D	F4: GAAGCAGTCCAGTGGGAGCCG (SEQ ID NO:101) R4: GCCTCCCCGGCTCCTCCTCAGG (SEQ ID NO:102)	Recognizes hC2D-specific insertion
5	hC2D	F3: GAGAGGCTGGCCCATCTGTATG (SEQ ID NO:99) R5: CCTCCACATCTGTTTCACTGTC (SEQ ID NO:103)	
6	hC2E	F5: CTCCATGATGGAAGACGTGGG (SEQ ID NO:104) R6: GATGAGCTCGTAGCGCTCGGC	Spans deletion unique to hC2E. Distinction based upon product size

		(SEQ ID NO:105)	differences following PCR
7	hC2B	F6: CATTGGCGTTTAAGCTCCTG (SEQ ID NO:106) R3: ATCTTCAAAGAATCCCTGCC (SEQ ID NO:100)	F6 primer spans deletion unique to hC2B
8	hC2A	F7: GGACCCATAGTTCATGATCG (SEQ ID NO:107) R4: CTTCATCTTCAAGAAATCCCTC (SEQ ID NO:108)	R4 primer spans the region where other CLASPs have an insert

Please replace the paragraph beginning on page 59, line 9, with the following amended paragraph:

In one embodiment, the antisense sequence is complementary to relatively accessible sequences of the CLASP-2 mRNA (e.g., relatively devoid of secondary structure). This can be determined by analyzing predicted RNA secondary structures using, for example, the MFOLD program (Genetics Computer Group, Madison Wis.) and testing in vitro or in vivo as is known in the art. Another useful method for identifying effective antisense compositions uses combinatorial arrays of oligonucleotides (see, e.g., Milner et al., 1997, Nature Biotechnology 15: 537). Examples of oligonucleotides that can be tested in cells for antisense suppression of CLASP-2 function are those capable of hybridizing to (i.e., substantially complementary to) the following positions from SEQUENCE ID NO: 1:

1) GAAGGCGATCATCACGTGGCCTTCCATCGC (SEQ ID NO:109)
2) GCTTCAAGTAATGACTGGTGCAGAACATCTG (SEQ ID NO:110)
3) GCTCCTCCTCAGGCAGGCGCTATGGCTGTGG (SEQ ID NO:111)
4) GTAGGCCCGGTGCAGCGTGTCATACAGATGG (SEQ ID NO:112)

(See also Example *8).

Please replace the table beginning on page 114, line 1, with the following amended paragraph:

Primer Table

CLASP gene	Sense Primer	Sense sequence	Antisense Primer	Antisense sequence
CLASP-7	HC7gS5	AGGCCTTGTCTCTGTTTACC TG (SEQ ID NO:140)	HC7gASI	TGTCATGTACTGCACTCGCACAGC (SEQ ID NO:145)
CLASP-7	HC7gS3	ACAGGAACCTGCTGTACGT GTAC (SEQ ID NO:141)	HC7AS14	TCGTGGCTGCACAGGATGCGGGTG (SEQ ID NO:146)
CLASP-4	C4P2	GACCCATTAGGAGGTCTAC (SEQ ID NO:142)	HC4AS3'	CGGGATCCATTGTCACCGTACATCT GC (SEQ ID NO:147)
CLASP-4	C4P2	GACCCATTAGGAGGTCTAC (SEQ ID NO:142)	HC4AS3'	CGGGATCCATTGTCACCGTACATCT GC (SEQ ID NO:147)
CLASP-1	hC1S5'	TATGTCTCAGTCACCTACCT G (SEQ ID NO:143)	HC1AS3' Kpn	CTTGGTACCACTTCAGCACTAGAT G AGATG (SEQ ID NO:148)
CLASP-1	C1S7	TCAAGACCAGGGCATGCAA G (SEQ ID NO:144)	HC1AS3' Kpn	CTTGGTACCACTTCAGCACTAGAT G AGATG (SEQ ID NO:148)

Please replace the paragraph beginning on page 114, line 3, with the following amended paragraph:

In-frame stop codons were not present suggesting that the cDNA was not full length. To obtain the 5' terminus of CLASP-2 5' RACE was employed. Antisense oligonucleotides directed against the 5' end of the longest CLASP-2 sequence were generated:

Primers used for human CLASP-2 5' RACE

primer	sequence (5' to 3')	nucleotide position
HC2RACE1	AAGAGCAGCATCTCCCGTAAACAGTC (SEQ ID NO:149)	-15 to 11

HC2RACE2	TAACAAGCTCTGTGCTTCCTCTTCCG (SEQ ID NO:150)	414 to 443
HC2RACE3	ACCACTTTGTTCGGAAGCTGTCGAAACTC (SEQ ID NO:151)	512 to 540
HC2RACE4	TTTGTACAGCCAGCCATGCTTGGTGATC (SEQ ID NO:152)	634 to 661

Please replace Table 5 beginning on page 121, line 11, with the following amended paragraph:

Table 5 below shows exemplary oligonucleotides for this assay:

Oligo	Sequence 5'-3'	length	notes/comments
1	GAAGGCGATCATCACGT GGCCTTCCATCGC (SEQ ID NO:109)	30-mer	encompasses nucleotides 473-502 and spans the putative initiator methionine (underlined). The function of HC2A, 2B, 2C, and 2E isoforms can be eliminated by this oligonucleotide.
2	GCTTCAAGTAATGACTGG TGCAGAACATCTG (SEQ ID NO:110)	31-mer	Oligonucleotide that should recognize HC2A, 2B, 2D, 2E, and 2F. Encompasses nucleotides 2121-2151. Can be eliminate function of these CLASP-2 isoforms.
3	GCTCCTCCTCAGGCAGGC GCTATGGCTGTGG (SEQ ID NO:111)	34-mer	oligonucleotide specific for HC2C based upon a specific exon found at nucleotide 2927. Can eliminate only HC2D function.
4	GTAGGCCCGGTGCAGCGT GTCATACAGATGG (SEQ ID NO:112)	31-mer	oligonucleotide specific for HC2B, 2C, 2D and 2E based upon specific exon sequence found at nucleotide 3153. Can eliminate function of these CLASP-2 isoforms.
5	GCAATGTCTGAGACTTTC GATCATGAACTATG (SEQ ID NO:113)	32-mer	oligonucleotide specific for HC2A, 2B, 2E, and 2F. Encompasses nucleotides 1987-2018. Can eliminate function of these CLASP-2 isoforms.

6	CAGGAGCTGGTTCTTAAA (SEQ ID NO:114)	18-mer	oligonucleotide specific for HC2A, 2D and 2B. Encompasses nucleotides 2219-2224. Can eliminate function of these CLASP-2 isoforms